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High incidence of initial and late steroid resistance in childhood nephrotic syndrome

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High incidence of initial and late steroid resistance in childhood nephrotic syndrome.

Background. Conventional wisdom states that greater than 80% of children with nephrotic syndrome (NS) respond to steroid treatment, remain steroid-sensitive during subsequent relapses, and consequently have a favorable long-term prognosis. In contrast, steroid resistance is believed to be associated with a high risk of developing chronic renal failure. Recent reports suggest that the histologic pattern of NS in children may be changing, but whether the change is accompanied by a parallel change in steroid sensitivity is unknown.

Methods. Initial and subsequent steroid responsiveness was evaluated in all children aged 1 to 18 years who presented with newly diagnosed NS to the 2 pediatric nephrology referral centers in southeastern Louisiana between 1994 and 2003. NS was defined as presence of edema, heavy proteinuria, and serum albumin concentration below 2.5 g/dL. Steroid sensitivity (SS) was defined as total resolution of proteinuria and edema, and partial response to steroids (PR) was defined as loss of edema with continuing proteinuria.

Results. There were 210 new cases of NS. Forty-one patients (20%) had immune complex glomerulonephritis. Six patients were excluded because of incomplete data availability. Of the remaining 163 patients, 115 (71%) were SS and 23 (14%) achieved PR during the initial 4 weeks of treatment; 25 (15%) were steroid-resistant (SR). Follow-up data were available for 91 of the 115 initially SS patients; 19 subsequently became steroid-resistant. Thus, at least 45% of the patients with new-onset NS did not have typical childhood steroid-responsive NS. Initial steroid resistance was more likely in African American children and in children with older age at onset (11.5 vs. 4.6 years). Development of steroid resistance after initial SS was associated with shorter interval to the first relapse (2.2 vs. 5.4 months) and having the first relapse during the initial steroid treatment.

Conclusion. Compared to previous reports, our results show a higher incidence of initial and subsequent steroid resistance, characteristics not consistent with typical minimal change NS with a benign prognosis. The results suggest that in the current era, NS in children may not be as benign as indicated by earlier studies.

Key words: childhood nephrotic syndrome, steroid resistance, MCNS, FSGS.

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Nephrotic syndrome (NS) is characterized by massive proteinuria and hypoalbuminemia, leading to edema and hypercholesterolemia. In contrast to adults, most children with NS have idiopathic nephrotic syndrome, rather than an NS secondary to an immune complex glomerulonephritis (ICGN). The most common causes of idiopathic NS in children are minimal change NS (MCNS) and focal segmental glomerulosclerosis (FSGS). The groundbreaking International Study of Kidney Disease in Children (ISKDC), on patients recruited from 3 continents between 1967 and 1976, was the first to report that MCNS is the most common histopathologic lesion in renal biopsies from children with idiopathic NS [1, 2]. In contrast, FSGS was a rare cause of NS in children, observed in only 5% to 7% of the biopsies [1–3]. ISKDC also established the standard initial treatment of idiopathic NS as 4 weeks of daily steroids, which has been reported to result in complete remission in 93% to 98% of MCNS patients but only in 17% to 30% of FSGS patients [3, 4], yielding an overall response rate in childhood idiopathic NS of over 80%. Development of steroid resistance after an initial remission (late steroid resistance) occurred in only 3.3% of the ISKDC subjects [5].

Several groups have determined the long-term prognosis for children with NS [6–8]. Minimal change histology and steroid responsiveness are usually associated with favorable prognosis with eventual resolution of the relapsing NS. In contrast, steroid resistance and FSGS histology often predict high risk of disease progression to chronic renal failure (CRF). Although not invariable, patients with steroid resistant NS often exhibit FSGS histology on biopsy.

There is evidence that the epidemiology of NS may be changing. While prior reports have shown that FSGS is infrequently detected in children with NS, some recent studies suggest that the incidence of FSGS is increasing in both pediatric and adult patients [9–14]. The reason for the apparent increase in incidence is unknown. Those reports did not systematically examine steroid responsiveness of the patients; hence, it is not clear whether the apparent change in histology is accompanied by parallel changes in sustained steroid responsiveness and long-term prognosis.

It has been our impression that in our patient population the incidence of steroid-resistant NS is higher than reported in the literature. To study this question, we evaluated the incidence of both initial and late steroid resistance in children who presented with new-onset NS between 1994 and 2003 to the 2 pediatric tertiary care centers serving our geographic area, and sought to identify factors predictive of steroid resistance in these patients.

METHODS

Patients

Retrospective chart analysis was done to identify all children who presented with new-onset NS to Children's Hospital in New Orleans and Tulane Hospital for Children in New Orleans between 1994 and 2003. These 2 centers serve as the only pediatric nephrology referral centers in an area of approximately 3 million people and 900,000 children. To avoid selection bias, only previously untreated, newly diagnosed patients were included. Patients less than 1 year of age (to exclude congenital NS) or over 18 year of age were excluded from this study.

Definitions and treatment

NS was defined as heavy proteinuria (urine protein/creatinine ratio >2.0), edema, and hypoalbuminemia (serum albumin <2.5 g/dL). All patients except those diagnosed with ICGN received standard treatment with daily corticosteroid (prednisone or prednisolone) at a dose of 2 mg/kg/day (maximum 60 mg/day) for 4 weeks and were then switched to alternate day therapy.

The response to initial treatment was defined after 4 weeks of daily steroid treatment as follows: (*1*) steroid-sensitive (SS), complete resolution of proteinuria and edema; (*2*) partial response (PR), resolution of edema and decrease, but not disappearance, of proteinuria; (*3*) steroid resistance (SR), no improvement.

The subsequent steroid responsiveness was evaluated during the first year following the initial presentation in patients who had at least 6 months of follow-up using the same criteria as for initial steroid responsiveness. The latest follow-up status of each patient is also reported; the total observation period ranged from 6 to 114 months.

Hypertension was defined as blood pressure higher than 95th percentile for age according to data from Task Force Report on High Blood Pressure in Children and Adolescents [15]. Hematuria was defined as a dipstick reading of 1+ or more for blood or as more than 3 red blood cells per high-power field in urine sediment. Estimated glomerular filtration rate (GFR) was calculated by the Schwartz formula: GFR = k × height (cm)/plasma creatinine (mg/dL), where k is 0.45 for infants (≤18 months of age), 0.55 for older children and adolescent girls, and 0.7 for adolescent boys over 13 years of age [16]. Decreased kidney function was defined as GFR <90 mL/min/1.73m^2, CRF as GFR <60 mL/min/1.73m^2, and end-stage renal disease (ESRD) as GFR <15 mL/min/1.73m^2 [17].

Pathology

In general, patients who were either suspected on clinical grounds of having NS other than MCNS, or who were not steroid sensitive underwent percutaneous renal biopsy. The diagnosis of ICGN was based on positive immunofluorescence and the presence of electron-dense "deposits" on electron microscopy. MCNS was characterized by the absence of any conspicuous abnormality on light microscopy. For the purposes of this report, FSGS was diagnosed either by the presence of at least 1 glomerulus showing a segmental area of sclerosis, or by prominent tubular atrophy and interstitial fibrosis without evidence of immune complex formation. Mesangial hypercellularity (MH) was defined by the presence prominent mesangial cell proliferation (more than 4 cells per mesangial area) with increased mesangial matrix without other conspicuous abnormalities.

Statistical analysis

All data are presented as mean ± standard deviation or as percentages. Comparison between 2 groups was done by Student *t* test and between multiple groups by one-way analysis of variance (ANOVA) with Tukey's post-test. Odds ratios of steroid resistance and 95% confidence interval were calculated by unconditional logistical regression. Nonparametric variables were analyzed using Kruskal-Wallis test or Mann-Whitney *U* test. Comparison of independent variables (current study vs. ISKDC data) was achieved by the Fisher exact probability test. Statistical significance was defined as $P < 0.05$. Statistical analyses were performed with GraphPad Prism Software for Science, version 3.00 (GraphPad Software, Inc., San Diego, CA, USA) and Stata 7.0 (Stata Corporation, College Station, TX, USA).

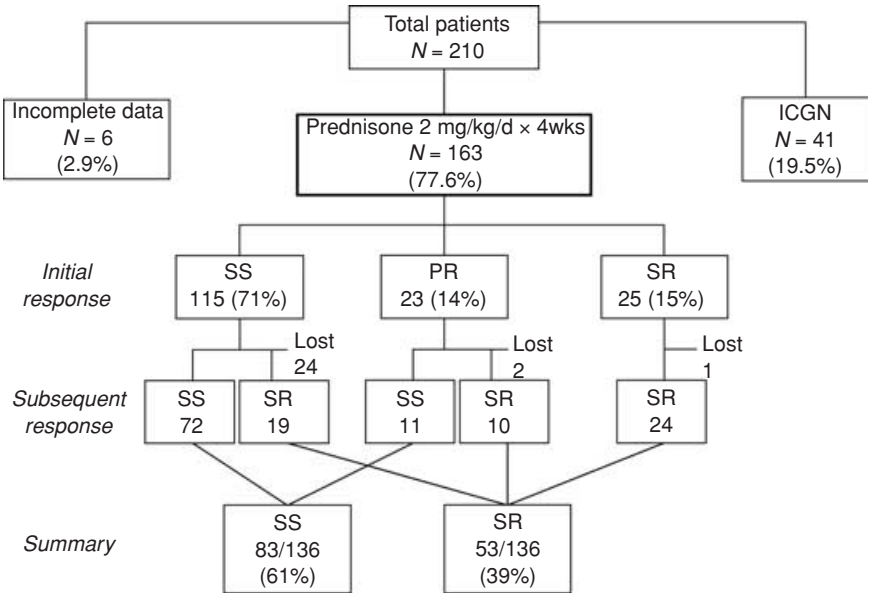

Fig. 1. Summary of patient data. ICGN, immune-complex glomerulonephritis; SS, steroid sensitive, PR, partial response to steroids; SR, steroid-resistant; lost, no follow-up data available. Initial response refers to response to the initial 4-week course of steroids. Subsequent response refers to steroid responsiveness during the subsequent course. Summary shows the total of SS, SR, and ICGN as a fraction of the 136 subjects in whom follow-up data were available.

RESULTS

Characteristics at onset

There were a total of 210 patients who presented with new-onset NS (Fig. 1), including those who had ICGN on biopsy. Of the total group, 108 were males (51%) and 102 were females (49%); 103 were white (49%), 96 were African American (46%), 6 were Asian (3%), 3 were Hispanic (1%), and 2 were of mixed ethnicity (1%). The mean age at onset of NS was 7.2 ± 5.2 years (range 1–18 years). The mean age of the African American patients at presentation was significantly higher than that of white patients (8.2 ± 5.2 vs. 4.3 ± 3.5 years, $P < 0.0001$). Fifty-eight patients had hypertension (28%) and 96 patients had hematuria (46%). The mean serum albumin concentration at presentation was 1.7 ± 0.5 g/dL and 36 patients (17%) had a reduced GFR. Six patients were excluded for lack of complete data.

Forty-one patients (19.5%) were found to have an ICGN (immunoglobulin A nephropathy, membranous nephropathy, membranoproliferative glomerulonephritis, or lupus nephritis). We did not include their data among the entire group to assess steroid-sensitivity because they all did not receive glucocorticoids for 4 complete weeks. Of the ICGN patients, 23 (56%) had hypertension, 31 patients (76%) had hematuria, and 13 patients (32%) had a decreased GFR. Hypertension, hematuria, and reduced kidney function were all more frequent in patients with ICGN than in the rest of the patients as a group ($P < 0.05$).

Initial steroid response

One hundred sixty-three patients with idiopathic NS received the standard initial treatment of 4 weeks of daily steroids. Initial complete remission was achieved in 115 patients (71%). Twenty-three patients (14%) had a PR and 25 (15%) were SR (Fig. 1). In those patients who achieved a complete remission, the mean time to response (disappearance of proteinuria) was 2.7 ± 1.3 weeks.

Table 1. Characteristics of patients with idiopathic nephrotic syndrome who were steroid-sensitive (SS), showed a partial response (PR), and were steroid-resistant (SR) after the initial 4 weeks of daily steroid therapy

	SS ($N = 115$)	PR ($N = 23$)	SR ($N = 25$)	P value
Sex (M:F)	61:52	14:8	11:14	0.50
Race (white:AA)[a]	65:43	15:6	6:18	0.004[b,c]
Age at onset *years*	4.6 ± 3.2	4.7 ± 4.3	11.5 ± 5.4	<0.0001[b,c]
Hypertension	16 (14%)	6 (26%)	10 (40%)	0.009
Hematuria	40 (35%)	11 (48%)	13 (52%)	0.41
Decreased GFR	9 (8%)	3 (13%)	8 (32%)	0.005
Albumin *g/dL*	1.6 ± 0.5	1.4 ± 0.5	1.8 ± 0.6	0.10

[a]For this particular data analysis, only white or African American patients were included.
[b]SS vs. SR.
[c]PR vs. SR.

Predictors of initial steroid responsiveness were evaluated as shown in Table 1. To assess the potential effect of ethnicity on response to steroids, we analyzed the rates of SS, PR, and SR in our 2 largest groups, whites and African Americans. We found that SR was more common ($P = 0.004$) than SS and PR in African American compared to white patients. However, when examined by unconditional logistical regression, ethnicity as an independent risk factor did not reach statistical significance.

For the rest of the parameters displayed in Table 1, patients from all ethnic groups who received 4 weeks of steroids were included. Age at onset was a highly

Table 2. Predictors of subsequent steroid resistance in patients with an initially steroid-sensitive idiopathic nephrotic syndrome

	SS ($N = 72$)	SR ($N = 19$)	P value
Sex (M:F)	39:33	8:11	0.42
Race (white:AA)[a]	39:29	13:6	0.61
Age at onset *years*	4.9 ± 3.5	4.4 ± 2.9	0.58
Hypertension	11 (15%)	4 (21%)	0.70
Hematuria	24 (33%)	9 (47%)	0.20
Decreased GFR	5 (7%)	3 (16%)	0.56
Albumin *g/dL*	1.6 ± 0.5	1.5 ± 0.5	0.60
Time to initial response *weeks*	2.6 ± 1.1	2.5 ± 0.9	0.91
1st relapse *months*	5.4 ± 3.8	2.2 ± 1.4	0.0006
1st relapse while on steroids	21 (29%)	14 (74%)	0.01

[a]For this particular data analysis, only white or African American patients were included.

significant factor; older children were more likely to be SR. SR patients had a higher prevalence of hypertension and decreased kidney function. Gender, presence of hematuria, and serum albumin level did not correlate with the response to treatment.

Subsequent steroid response

Twenty-four patients who were initially steroid-responsive were lost to follow-up. Of the 115 children who were initially steroid-sensitive, 72 (63%) continued to respond to steroids (Fig. 1). A surprisingly large number (19 patients, or 17%) developed steroid resistance during subsequent relapses despite being initially steroid responsive. Of the 23 initial partial responders, 11 patients achieved complete remission with prolonged steroid therapy and later remained SS. Ten patients developed steroid resistance, and 2 were lost to follow-up. Except for 1 patient who was lost to follow-up, all of the patients who were initially SR continued to be steroid resistant throughout the study period. In summary, 53/136 (39%) of the patients continued to exhibit or developed steroid resistance. Sustained SS was documented in 83/136 (61%), and if all 24 initially SS who were lost to follow-up are assumed to have remained SS, the percentage of subsequent SS patients may be as high as 66%. Overall, 94/210 (45%) of patients with new-onset NS had either ICGN or long-term steroid resistance, suggesting a poor prognosis.

Predictors of late steroid resistance were assessed in patients with initial complete remission (Table 2). Ethnicity did not predict late steroid resistance. The time period required for the initial response to steroid treatment was virtually identical between those who remained SS and those who developed late SR. In contrast, the time interval from the initial response to the first relapse was significantly shorter in patients who developed late steroid resistance, 2.2 months versus 5.4 months in patients who continued to be steroid-sensitive ($P = 0.0006$). In addition, patients who developed late steroid resistance were significantly more likely ($P = 0.01$) to experience first relapse while receiving steroids. Gender, age at onset, hypertension, hematuria, serum albumin, or kidney function at onset did not predict late steroid resistance.

Table 3. Summary of steroid responsiveness and resistance in the current study and in comparison with ISKDC data

	Current study	ISKDC
Age at onset *years*	7.2 ± 5.2[a]	4.8 ± 2.9
Initial responsiveness% [b]	70.6[a]	86.3
Late resistance% [c]	16.5[a]	3.3

[a]$P < 0.0001$ vs. ISKDC data.
[b]Excluding patients with ICGN from both studies and comparing patients who were steroid-sensitive with complete resolution of proteinuria; source of ISKDC data: reference #4
[c]Source of ISKDC data from [5].

Comparison of current data with ISKDC

We sought to compare the rates of initial steroid responsiveness and late steroid resistance in our patients to those included in the ISKDC data [4, 5]. It is important to note that throughout our study we excluded all patients with ICGN. In contrast, the ISKDC included patients with ICGN in their analysis of initial steroid-responsiveness [4] but excluded patients with ICGN in their subsequent analysis of late steroid responsiveness [5]. Thus, a direct comparison between the incidence of initial steroid responsiveness between our and their study population could only be done accurately if we eliminated patients with ICGN from their original study. In summary, we observed a significantly lower rate of initial steroid responsiveness in our patients. Moreover, even assuming that all patients lost to follow-up who were initially steroid-responsive remained responsive, we still observed a significantly higher rate of late steroid resistance in our patients compared to the IDSKDC patient population (Table 3). However, the age at presentation of our patient population was significantly higher than that reported by the ISKDC [4].

Histopathology

Forty-one patients had ICGN on biopsy. The histologic diagnoses included lupus nephritis (13 patients), membranoproliferative glomerulonephritis [12], membranous nephropathy [11], IgA nephropathy [3], and other immune complex glomerulonephritis [2].

Renal biopsy was done in most patients who did not exhibit sustained steroid responsiveness. Of 23 partial responders, 14 patients (61%) underwent renal biopsy. Of these, MCNS was diagnosed in 36%, MH in 43%, FSGS in 21%. Twenty-four of the 25 patients (96%) who were initially SR had a renal biopsy done. Of these patients, MCNS was present in 17%, MH in 8%, and FSGS in 75%. All the 19 patients with late steroid resistance who were

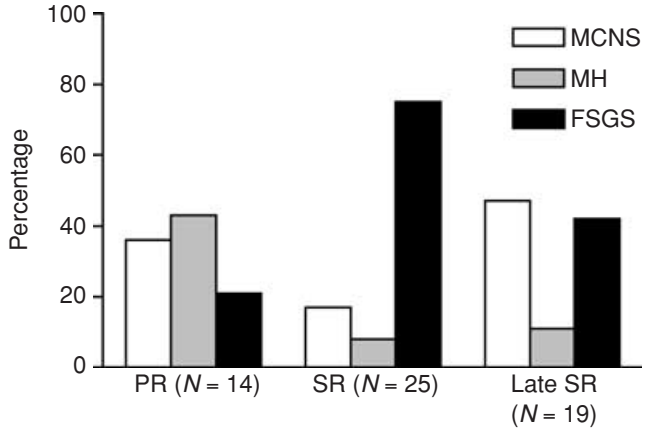

Fig. 2. Histologic findings in the patients with initial partial response (PR), initial steroid resistance (SR), and late steroid resistance (late SR). FSGS, focal segmental glomerulosclerosis; MH, mesangial hypercellularity; MCNS, minimal change nephrotic syndrome.

initially SS underwent renal biopsy; MCNS was observed in 47%, MH in 11%, and FSGS in 42% (Fig. 2).

The latest follow-up status

Most patients with idiopathic NS who were resistant to oral steroids received other antiproteinuric medications. These included angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, alkylating agents (cyclophosphamide or chlorambucil), high-dose intravenous steroids (e.g., "pulse methylprednisolone"), and calcineurin inhibitors (cyclosporine or tacrolimus).

The latest follow-up status was available in 136 of the 163 (83%) patients with idiopathic NS, as shown in Table 4. The follow-up period of these patients ranged from 6 to 114 months. One hundred and ten patients were either in prolonged remission or continued to have relapses; all previously SS patients were included in this group. Of the 53 previously SR patients, 21 patients had unremitting NS with normal renal function, while 5 patients developed CRF, including 2 who progressed into ESRD. All 5 patients who developed CRF were African American, initially and subsequently SR, and had a renal biopsy showing FSGS.

Table 4. The latest follow-up status of 136 patients with idiopathic nephrotic syndrome according to early clinical course

	Steroid sensitivity during the first year after diagnosis	
Latest status	SS ($N = 83$)	SR ($N = 53$)
Prolonged remission or continuing relapses	83 (100%)	27 (51%)
Unremitting NS		21 (40%)
CRF		3 (5%)
ESRD		2 (4%)

DISCUSSION

Childhood NS was once considered a benign condition because of the good response to steroid treatment in the vast majority of patients. Indeed, a comprehensive review of childhood NS showed that the response rate of childhood NS to steroids has been reported to be at least 80% in previous studies [18]. Our findings differ from the results of those studies in several important aspects. First, we observed a relatively high (20%) incidence of ICGN in patients with new-onset NS. Another major finding derived from our study is the relatively lower rates of initial steroid responsiveness compared to the ISKDC studies. For our analysis of initial steroid responsiveness, we excluded all patients with ICGN. In contrast, the ISKDC included patients with ICGN in their analysis of initial steroid-responsiveness [4] but excluded patients with ICGN in their subsequent analysis of late steroid resistance [5]. Thus, a direct comparison between the incidence of initial steroid responsiveness between our and their study population could only be done accurately if we eliminated patients with ICGN from their original study. Excluding all patients with ICGN, the response rate in our patients to the initial course of steroids was 71%. In contrast, 86% of patients with NS but without ICGN responded to the initial course of steroids in the ISKDC study [4]. It is important to re-emphasize that although initial steroid-responsiveness was reported by the ISKDC to be 78%, this figure included patients with ICGN.

Another significant difference between our and the ISKDC study is that according to current practice standards, all of our patients received 4 weeks of steroids during the initial presentation of NS compared to some patients in the ISKDC study who received 8 weeks of steroids. One could argue that the lower rates of initial steroid-responsivenes in our patients may be due, in part, to the shorter course of steroids received by some of our patients. However, close analysis of the ISKDC data reveals that very few patients in the ISKDC study achieved remission after the initial 4-week period [4]. Finally, the progression to steroid resistance after initial steroid responsiveness, a rare occurrence in previous reports, was relatively common (17%). This was significantly higher than reported by the ISKDC [5]. Overall, 45% of newly presenting NS patients did not have typical steroid-responsive childhood NS.

Thus, our data, collected on patients who presented during the most recent decade, strongly suggest that the epidemiology of steroid responsiveness in childhood NS is changing. We believe that our results reflect the true epidemiology of NS in our population for the following reasons. First, our 2 centers are the only pediatric nephrology referral centers in southeastern Louisiana,

and our informal survey has established that almost all pediatric patients with NS are referred by the primary care physicians. Second, including only previously untreated patients removes the possibility of selection bias toward steroid-resistant patients. Based on our data, we estimate that the minimum incidence of childhood NS in our geographic area is approximately 2.3 new cases/10^5 children per year; it may be slightly higher because we excluded a few patients who were previously treated by their primary care physician. This incidence is comparable to the previously reported incidence of childhood NS of 2.0 new cases/10^5 children per year in the United States [19] and slightly lower than a recently reported incidence from Canada [11]. Thus, it appears that there has not been a large increase in the incidence of NS in general, but that there may be a shift toward steroid resistance.

Predictors of initial steroid resistance in our study were age at onset, hypertension, and decreased kidney function. Older age at the time of initial presentation was associated with a higher risk of steroid resistance. The age of our patients at presentation was significantly higher than the cohort included in the ISKDC study [4]. We hypothesize that age may have been a very important factor in determining the higher incidence of steroid resistance in our patient cohort compared to the ISKDC. Indeed, Baqi et al reported that FSGS is more common in older (older than 6 years of age) versus younger (less than 6 years of age) children with NS [23]. Thus, our results are consistent with prior reports showing that older children and adolescents have a higher incidence of FSGS and steroid resistance [4, 22].

Another major factor that may have resulted in the higher rate of steroid resistance in our patients was the high proportion of African American patients in our study population compared to the ISKDC population. However, although African Americans are reported to have a higher incidence of FSGS [20, 21], the association of age with steroid resistance in our material was still present after corrected for ethnicity. This is in agreement with the described increase in FSGS in Caucasian children in Canada [11]. Even though ethnicity did not reach statistical significance as an independent risk factor for steroid resistance in our subjects, this may be due to the limited number of subjects. Forty-six percent of our patients were African Americans and they comprised the majority of those who were steroid-resistant. Thus, it seems reasonable to state that the higher incidence of initial steroid-resistance in our study versus the ISKDC is likely due, in part, to the higher percentage of African American patients in our cohort. In contrast, our data suggest the incidence of late steroid resistance is not affected by ethnicity. One major confounding factor in the analysis of the effect of ethnicity on steroid resistance is the fact that the age at presentation of our African American patients was almost twice that of the white patients; thus, it seems reasonable to speculate that a major factor causing the higher rate of steroid resistance in our patient population is the combined effect of ethnicity and older age.

An important new finding in our study was the surprisingly high number of patients who developed late steroid resistance during subsequent relapses despite being initially steroid responsive. This subsequent resistance usually occurred between 1 month and 1 year after the initial episode. There are scant reports describing late steroid resistance in children with NS, all studied before 1990 [5, 6, 24, 25]. Those reports show that only 1% to 5% of children with NS develop late steroid resistance after initial steroid responsiveness. For example, the ISKDC study reported that only 3.3% of initial responders developed late steroid resistance [5]. We assessed various potential predictors of late steroid resistance in our patients. We found that an early relapse after the initial remission and the occurrence of the first relapse while receiving the initial course of steroids were predictive factors for late steroid resistance. Ethnicity was not predictive of late steroid resistance, although it did predict initial steroid responsiveness.

Until recently, MCNS has been considered the predominant pathology in children with NS. However, since 1999, several reports have suggested that the incidence of FSGS may be increasing in children and adults [9–14]. According to those reports, FSGS is now estimated to account for 22% to 46% of childhood idiopathic NS. Because the present study was not a prospective investigation including renal biopsies in all patients, we cannot make any definitive statements regarding the overall incidence of FSGS, or the relationship between steroid resistance and histopathology. However, we did observe that a majority of patients who were steroid-resistant and who had a renal biopsy performed had FSGS. Interestingly, almost half of the patients with partial response to steroids showed MH on biopsy, which has been suggested to be an early marker for developing FSGS [26, 27]. Moreover, a significant percentage of steroid-resistant patients had MCNS histology; this agrees with previous reports that have shown that minimal change histology is not invariably associated with steroid responsiveness [28], sometimes progressing into FSGS on follow-up biopsies [27, 29, 30].

The follow-up period of our report is not long enough to determine the long-term prognosis, especially the percentage of patients progressing into ESRD. However, unremitting NS or proteinuria is generally considered a poor prognostic sign in idiopathic NS. Despite the relatively short follow-up, 5 patients developed renal failure or ESRD; all had been classified as steroid-resistant. At the latest follow-up, 81% were either in prolonged remission or continued to have relapses while 19% remained resistant to all treatment. Some patients who

were initially steroid resistant apparently responded to other immunosuppressive medications. However, all of the patients who had unremitting NS at the latest follow-up had been steroid resistant at some point during the entire first year of analysis. Based upon this observation, we speculate that steroid responsiveness during the first year likely predicts each patient's subsequent course. The ISKDC study [5] also reported that the early course is one important factor predicting the ultimate outcome.

CONCLUSION

Our data show that steroid-responsive idiopathic NS is less common in children with newly diagnosed NS than previously reported. The reasons for the change in epidemiology are not clear, but it does not appear to be due to overall increase in the incidence of NS in childhood. Hence, we conclude that the risk of steroid resistance in childhood NS may be higher than generally believed. This may have implications for long-term prognosis.

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